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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,977	NGUYEN ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 45-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 45-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) . Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

JL

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group 1 (claims 1-10 and 13-16) is acknowledged. The traversal is on the ground(s) as to the restriction of Groups I claims from those of Group II. Applicants request that the Examiner combine these claims into a single group. The steps of Groups 11, drawn to a method for identifying a protease which cleaves a substrate sequence, and I remain the same regardless of the substrate sequence used. Therefore the claimed steps are capable of use together. The claimed steps have the same or similar modes of operation. And the claimed steps have the same functions and the same effects, which are to identify a protease, which cleaves a substrate sequence.

In view of applicants' request and arguments, Group II (claims 11 and 12) will be joined with Group I (claims 1-11 and 13-16).

Applicants' election of the following subspecies is also acknowledged. The elected species are as follows: (A) N is a positive integer between 1-20; (B) the granzyme B protease scaffold; and (C) cancer as the pathology.

Status of Claims

Original claims 1-16 and newly added 45-58 are pending and under examination.

Specification

The specification is objected to because of the omission of Seq. ID. Nos. in the sequences at e.g. page 51, lines 15-20; page 22, line 15. Applicants are requested to check for other sequences in the specification since they are too numerous to mention specifically.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors (typographical, grammatical and idiomatic). Applicants' cooperation is requested in correcting any errors of which applicants may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 and 45-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written

description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite for a method of identifying a protease that cleaves a substrate sequence comprising producing a library of mutein protease sequences with each member having N mutations relative to the wild type scaffold and N is 1-20. To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The disclosure at the time of filing does not describe the huge scope of the claimed components in the method. The claimed genus covers a huge scope for the enzyme and its mutants thereof that forms a library. The claims do not provide a structure for any of the components. It does not recite the kind and location of amino acid residues that can replace the original residue to result in a mutein of a library. The disclosure at page 3 recites a diverse number of mutations made in the enzyme scaffold. It provides and lists the different protease enzymes, pathology and target. A laundry list disclosure of every possible moiety does not constitute a

written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967). The illustrative Examples, that provide the detailed description of the invention is drawn to a single, defined species of the component method. The specification discloses that for a specific type of protease as serine proteinases, the enzymes exhibit different substrate specificities, which are related to amino acid substitutions in the various enzyme subsites interacting with the substrate residues. Some enzymes have an extended interaction site with the substrate whereas others have a specificity restricted to the P1 substrate residue. Three residues which form the catalytic triad is essential in the catalytic process i.e. His 57, Asp 102 and Ser 195. It seems likely, given the early stage of the field, that more roles exist [for caspase, a cys protease]. Caspases and caspase regulators involved in these processes may be missed in screens that focus strictly on t-5 cell death related phenotypes. Thus, molecules that possess caspase or caspase regulatory activity may not have been identified yet. For the cysteine proteases, the amino acids selected to be modified are less well described. One therefore cannot immediately envisage from the single species the genus as

claimed. The knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. The more unpredictable the art, as discussed above, the greater the showing required e.g. by (representative examples) for adequate disclosure. Adequate disclosure, like enablement, requires representative examples, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that applicant had possession of the full scope of the claimed invention (genus).

Possession of the claimed invention is shown by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed (genus) invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQM 1961, 1966 (Fed. Cir. 1997); MPEP 2163.

Claims 1-16 and 45-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(1) the breadth of the claims,
(2) the nature of the invention,
(3) the state of the prior art,
(4) the level of one of ordinary skill;
(5) the level of predictability in the art,
(6) the amount of direction provided by the inventor,
(7) the existence of working examples, and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, (U.S.P.Q. 2d 1400 (CAFC 1988).

1). The specification fails to give adequate direction and guidance in how to readily go about determining the mutations that can be done to a scaffold of any protease to produce a library of muteins.

2). The specification failed to provide working examples for any of the numerous and different type of mutations in the protease or the library of muteins of such broad scope (i.e., of undefined structure for the library or specific mutations of amino acids for a protease.)

3). The breadth of the claims encompasses a large diversity of mutant protein, the predetermination of the sites of variations in a protein or the amino acids involve in the variation. It is well known in the art, that it is often

difficult to know where insertions in the protein for mutations can be done without deleteriously affecting the protein function or its global structure. The diversity of the inserts is not easily estimated. It may be for example, that only a small subset of possible peptide sequences are presented efficiently by a particular expression system. And, it is not always easy to follow the expression of peptides in particular cells; for example, to know whether or not a specific cell is expressing a member of the insert, especially for biological methods.

4). The state of the prior art is such that techniques are specifically applied for a predetermined protein and mutations thereof.

5). The art is inherently unpredictable because it is not possible to predict which predetermined (variations) of amino acids would result in the desired random mutant with a desired pharmacologic activity. See further the discussion above. It is generally known that the conformational freedom that promotes binding, e.g., by modifying the peptides into the protein sequences, might be restricted which may likely perturb the function and stability of the protein in ways difficult to predict and measure. Some proteins accommodate insertions (variations) at numerous sites throughout their primary sequence. Others are much less accommodating. It is difficult in general to predict which proteins are robust to insertions, and

which sites in a particular protein are best suited to insertion of multiple independent sequences. The complex spatial configuration of amino acid side chains in proteins and the interrelationship of different side chains in the randomized sites are insufficiently understood to allow for such predictions. Selective (site-directed) mutagenesis and saturation mutagenesis are of limited utility for the study of protein structure and function in view of the enormous number of possible variations in complex proteins. There are still no rules that have emerged that allow structure to be related to sequence in any simple fashion (even as applied to the actual compounds).

6). Because the art is unpredictable, applicants' specification reasonably would not have assured persons skilled in the art that the numerous (undefined) variables of the claim would result in a mutations having a pharmacologic activity without undue experimentation. Applicants do not adequately enable persons skilled in the art to readily determine such. Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 45-58 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The amendment to he claims canceling "protease scaffold" renders the claim unclear in reference to the claim "N mutations relative to a wild-type scaffold". "The activity " in step (b) lacks antecedent basis of support from the preceding steps.

2. Claim 7 is unclear as to whether the protease scaffold refers to the wild-type recited in claim 1 (the scaffold not directed to the wild-type has been cancelled.)

3. Claim 10 phraseology "in a way" is unclear as to the means it is involved in pathology.

4. Claim 46 is indefinite as to the reference of the "earlier reiteration" i.e., as to which reiteration is considered earlier.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16 and 45-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Harris et al (The Journal of Biological Chemistry) alone, or Harris in view of Bianchi et al (Biopolymers).

Harris et al discloses at page 27364, a method of identifying optimal substrate specificity for proteases as granyzme B that allows for the identification of in vivo substrates in the process. The method comprises using the combinatorial methods of synthetic substrate libraries and substrate-phage display for an optimum substrate for granzyme B that spans over six subsites. Granzyme B proteolysis was shown to be highly dependent on the length and sequence of the substrate. Supporting the role of granyzme B preferred substrate sequence matches the activation sites of caspases 3 and 7 that is consistent with the role of granzyme B in the activation of

these caspases during apoptosis. Many caspase substrates contain granzyme B cleavage site and are potential granzyme B targets. Harris at page 27364 discloses construction of granzyme B variants of R192A and R192E. Harris does not disclose a combinatorial library mutant for the enzyme granzyme B. However, Bianchi at page 112, col.1 and col. 2 discloses that the use of peptide libraries in protease drug discovery has often been limited to substrate optimization, rather than to inhibitor (i.e., enzyme) optimization. Bianchi discloses the numerous advantages in the used of the combinatorial library of enzymes. It would have been obvious to one having ordinary skill in the art at the time the invention was made to make a library of the enzyme (inhibitor) in the method of Harris replacing the library of substrate as taught by Bianchi. The numerous advantages provided by Bianchi and the beneficial effect of changing from a substrate library to an enzyme library would motivate one to make said changes. Furthermore, the disclosure of Harris of the different variants of granzyme could read or would lead one to a combinatorial library of said enzyme.

Claims 16, 45-46 and 53 are obvious over the disclosure of Harris of the known iterative process of phage display method. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw

March 18, 2005